Managing Exacerbation of Asthma: Pharmacologic Therapy

JMAJ 45(9): 381–387, 2002

Koichiro KUDO

Vice Director, International Medical Center of Japan

Abstract: The deterioration of asthmatic conditions is divided into “symptom” and acute exacerbation. “Symptom” is a pathological state in which the contraction of bronchial smooth muscles is observed predominantly, and acute exacerbation is considered to be a more serious condition in which a severe inflammation of the airways is observed. The basic drugs used for treatment of these pathological states include bronchodilators, corticosteroids, and oxygen. For mild symptoms, bronchodilators such as inhaled \( \beta_2 \)-agonists are used as a quick reliever. When the symptoms are relieved, treatment is considered successful. When the symptoms cannot be relieved or deteriorate rapidly, the condition is judged as acute exacerbation, and bronchodilators and systemic corticosteroids are used together, as well as oxygen if necessary. It is essential to make the patients understand the difference between these two pathological states and the difference between the treatments for each state, and the importance of a prompt judgment of the pathological state. The short-term use of oral corticosteroids in acute exacerbation is possible under patient self-management and is highly useful.

Key words: Acute exacerbation; Symptom; Bronchodilators; Systemic corticosteroid; Oxygen therapy; Patient education

Definition of Terms

Asthma is both a chronic inflammatory disease of the airway and a disease with acute exacerbation. To treat asthma, either long-term control or quick relief medication is selected according to the pathological state. Prompt judgment and treatment are needed when there is deterioration of the disease.

The term “acute attack” is used conventionally; lately, “acute exacerbation” has also come into use. The two terms are nearly synonymous.

The international guidelines recommend that distinction should be made between the acute exacerbation of asthma and the “symptom” of asthma. This means that the nature of the symptoms of asthma should be broadly classified and should be managed accordingly.
The above-mentioned “symptom” is included in the “mild” classification. When the patient experiences difficulty in talking or shows agitation and cyanosis, the state is referred to as “severe”; if there is mental confusion, somnolence, disturbed consciousness, incontinence, and respiratory arrest, the state is evaluated as “serious”.

For a mild acute exacerbation, home treatment by self-management is possible. For moderate, severe and serious acute exacerbation, appropriate management such as treatment in an emergency room or hospitalization is necessary.

**Pharmacologic Therapy**

Pharmacologic therapy for asthma is basically the combination of a corticosteroid and a bronchodilator, and administration of oxygen (Table 2).

The following methods for corticosteroids treatment are used: (1) Administration of an inhaled corticosteroid at a dose 2 or 3 times higher than the usual dose, (2) intensive use of...
an oral corticosteroid, and (3) intravenous administration. For mild severity, method (1), and for moderate or more severe severity, methods (2) and (3) are selected, respectively.

Treatment method with bronchodilators includes β2-agonists, inhalation, subcutaneous injection of β2-agonists, intravenous administration of aminophylline and subcutaneous injection of epinephrine. Epinephrine has both pharmacological activity of a β-action inducing bronchodilation and an α-action suppressing bronchoedema.

Oxygen is administered using a nasal cannula, face mask and respirator. Recently, it was reported that the noninvasive BiPAP method is also effective. Oxygen is administered while monitoring with a pulse oximeter to keep Spo2 at not less than 90% or Pao2 at not less than 80torr.

These drugs are combined, and the dosages and administration frequency are determined in accordance with the severity of symptoms.

The practical applications of pharmacologic therapy are described below.

1. Initial treatment

   (1) For mild symptoms

The use of an inhaled β2-agonist is the first choice. This method can relieve symptoms rapidly and act quickly. A metered dose inhaler (MDI) is sprayed 2 to 4 times into a spacer which a patient is supposed to inhale. When a sufficient response cannot be obtained, inhalation is repeated every 20 minutes for 1 hour.

A patient is allowed to go home when PEF reached at more than 60% of the personal best value. In this case, short-term treatment with an oral corticosteroid is instructed, and if this medication does not relieve symptoms, prompt visiting outpatient clinic should be recommended.

An oral corticosteroid should be continued once a day or twice a day in a daily dose equivalent to 20–30 mg of prednisolone until the peak expiratory flow value returns to the personal best value.

(2) For moderate or more severe symptoms

1) Inhalation of β2-agonist using a nebulizer: When inhalation of β2-agonist with the aid of a spacer is possible, it may be done in the same manner described in the previous section, but when it is difficult due to severe conditions, the use of a nebulizer is effective.

   Dose: salbutamol 5 mg (ex. 1.0 ml of 0.5% Venetin® solution) + 10–15 ml of physiological saline with ultrasonic nebulizer. When the response to a dose of inhaled β2-agonist is insufficient, the same treatment is repeated every 20 minutes for 1 hour followed by repetition every 60 minutes (Table 3). If any side effect due to an excessive dose is observed, treatment is interrupted temporarily. The frequent use of inhaled β2-agonists for chronic asthma generally causes fewer side effects.

2) The switch to intravenous administration of aminophylline may be effective. Although there is a tendency to avoid the use of aminophylline because of the narrow range of effective concentrations (10–20 μg/dl) and the possible occur-

<table>
<thead>
<tr>
<th>Severity</th>
<th>Inhaled β2-agonist</th>
<th>Subcutaneous administration of Bosmin®</th>
<th>Intravenous administration of aminophylline</th>
<th>Steroids</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>☀</td>
<td>×</td>
<td>△</td>
<td>△△□</td>
<td>△</td>
</tr>
<tr>
<td>Moderate</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
</tr>
<tr>
<td>Severe</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
</tr>
<tr>
<td>Serious</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
</tr>
</tbody>
</table>

☐ Definitively indicated, ☀ Indicated, △ Not definitively indicated, but can be used, × Not indicated
rence of serious side effects in high concentrations, treatment with aminophylline is less difficult and useful method once it is learned how to use it safely. For safe administration, it is given over 20 to 30 minutes to obtain and then maintain the effective concentration of the drug (Fig. 1). A relatively easy method is described below.

The loading dose (LD) is 6 mg/kg, and the drip infusion rate (DIR) is 0.6 to 0.8 mg/kg/hr, respectively (the average values derived statistically from a multitude of examples). If possible, the blood concentration is monitored at a few points in time after administration, and the DIR is adjusted to gain the optimal concentration of aminophylline. Again to ensure safe treatment, it is necessary to take 20 to 30 minutes for the intravenous administration of LD.

With regard to theophylline, various factors affecting the blood concentration have been reported. For example, the blood concentration rises in heart failure, liver diseases, and viral infection, as well as in the concomitant use with macrolides. It decreases in smokers. Since theophylline is metabolized by the drug-metabolizing enzyme P450 in the liver, it is influenced by concomitant used-drugs and the pathological state of patient. For more detailed information, see the established literature.

3) Subcutaneous administration of epinephrine is used for moderate or more severe asthma exacerbation. This drug is injected subcutaneously at a dosage of 0.2 to 0.3 ml. As far as pulse rate is less than 130/minute, repeated administration every 20–30 minutes is possible. For serious or life-threatening conditions, it is administered at a dosage of 0.3 to 0.5 ml. This drug,
with both \( \alpha \)-action and \( \beta \)-action, acts quickly. Its \( \alpha \)-action reduces bronchoedema and its \( \beta \)-action induces bronchodilation. Epinephrine is contraindicated in the presence of hyperthyroidism, ischemic heart disease, or glaucoma. The use of this drug is also contraindicated in dehydration and should be avoided during pregnancy.

4) Corticosteroid therapy: When corticosteroids are used to treat acute exacerbation of asthma, these drugs tend to be administered at insufficient doses due to fear of the general side effects of steroids, or at excessive doses in order to intend to improve the symptoms quickly. The standard method including appropriate dosage is recommended in the guidelines. Generally, the side effects of corticosteroids occur when they are administered systemically and for a long term. The period during which steroids are used for acute exacerbation would be relatively short.

It is important in acute exacerbation to use the appropriate amounts of corticosteroids without concern about their side effects, but with several cautions. That is because acute exacerbation of asthma is a state in which the inflammation has progressed markedly, and because corticosteroids are the most potent drugs in inflammation of asthma.

The guidelines recommend short term treatment with oral corticosteroids (Table 4). In Japan, corticosteroids are administered at a dose of 0.5 mg per kg of body weight in the form of prednisolone (PSL) for about 1–2 weeks, until PEF returns to the personal best value. Subsequently, the basic treatment for the patient, that is, the use of a regular dose of an inhaled corticosteroid or a regular dose of an oral corticosteroid, is substituted without tapering process.

The necessary corticosteroid amount should be prescribed in advance, and the patients should be educated to take oral corticosteroid by their decision when they experience such states as listed in Table 4. In this way, the patient will feel secure, will learn how to prevent serious acute exacerbation, and will acquire self-management skills.

With regard to intravenous administration method: Administration of hydrocortisone or methylprednisolone starting from 200–500 mg or 40–125 mg as a loading dose, respectively, followed by 200 mg or 40–80 mg, respectively, is added every 4–5 hours for moderate or more severe acute exacerbation.

With regard to the side effects of corticosteroids to be kept in mind as mentioned below:

First, patients with diabetes complicated with asthma are in danger of increasing their blood sugar level, occasionally resulting in ketosis. For these patients, hospital treatment

<table>
<thead>
<tr>
<th>BMJ 1993 S3: Rescue use of Cs tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. When symptoms or PEF deteriorates on a daily basis</td>
</tr>
<tr>
<td>2. When PEF is 60% of the personal best value or lower</td>
</tr>
<tr>
<td>3. Somnopathy</td>
</tr>
<tr>
<td>4. When morning symptoms continue during daytime</td>
</tr>
<tr>
<td>5. When the response to bronchodilators becomes weaker</td>
</tr>
<tr>
<td>Adult: equivalent to 30–60mg/day of PSL, for 2 days after the symptoms are controlled, then, administration is interrupted or the dosage is reduced</td>
</tr>
<tr>
<td>Children: equivalent to 1–2mg/kg of body weight of PSL, for 1–5 days, then, administration is interrupted</td>
</tr>
</tbody>
</table>

* Japanese guidelines 1998 (by the Japanese Society of Allergology) |
* Equivalent to approximately 0.5mg/kg of body weight/day of PSL, for 1–2 weeks, then administration is interrupted or the dosage is reduced

* Cautions in diabetes—an increase in blood sugar level or ketosis is caused.
using insulin should be determined, since treatment under self-management or on an outpatient basis is difficult. Luckily, treatment with inhaled corticosteroids never increases blood sugar level.

Second, bolus intravenous administration of large doses of corticosteroids in patients with aspirin-induced asthma requires another caution. Aspirin-induced asthma is a disease that involves acute exacerbation occurring immediately after administration of aspirin, pilin derivatives or acidic nonsteroidal anti-inflammatory drugs, and it is said to account for approximately 5% of adult asthma cases. Bolus intravenous administration of large amounts of succinate corticosteroids (for example, hydrocortisone, methylprednisolone, and prednisolone) or steroids containing paraben preservatives is considered to induce asthma exacerbation.

When the presented case is aspirin-induced asthma or when the presented ease is not certain about complicity with aspirin-induced asthma, the use of such steroids should be avoided. To be enough safer from serious side effects, phosphate corticosteroids (ex. beta-methasone, dexamethasone) should be used instead, or succinate corticosteroids, if used, should be given slowly (taking 1–2 hours) via drip infusion, not via bolus intravenous injection to prevent side effects.

5) Hospital treatment: When hospitalization is required because initial treatment did not result in satisfactory improvement, the same initial treatment should be continued also in the hospital in principle. In serious conditions such as near death, management with a respirator or systemic management should be performed with adequate pharmacologic therapy. If the symptoms are still not improved and expectoration is caught extensively in the lumen of bronchi, the use of inhalation anesthetics such as isoflurane and enflurane followed by washing of the bronchi may be effective. In such cases, it is necessary to treat the patient in cooperation with anesthesiologists.

Treatment During Recovery Phase from Acute Exacerbation

The transition from acute phase to recovery phase is evaluated on the basis of peak expiratory flow value returned to at least 75% of the personal best value, or a daily variability in peak expiratory flow value of 25% or less. Reaching these values, therapy is switched from drip infusion treatment to oral treatment at reduced dosages, and finally returned to the regular treatment.

An example is given here: for steroids, drip infusion is switched to oral administration at a dosage equivalent to 20–30 mg/day of prednisolone, and then to inhalation of corticosteroids; for theophyllines, drip infusion is switched to oral administration; inhaled β₂-agonists are given on an on-demand basis; administration of oxygen is interrupted when Spo2 reaches 95% or Pao2 reaches 80 torr.

Various Questions Concerning Treatment Methods

1. Inhalation of β₂-agonists or drip infusion of Aminophylline

As discussed, there are several treatment methods aiming at bronchodilation. No conclusion has been determined yet as to which one of these is best. Treatment with inhaled β₂-agonists is easy to use and works quickly. To gain the efficacy of drip infusion of aminophylline, theoretical calculations for optimal serum concentration must be learned. The pharmacological efficacy of aminophylline for asthma are not only bronchodilating but also stimulus on respiratory muscles and respiratory center. Some reports have indicated that there is no difference in efficacy between treatment with inhaled β₂-agonists, treatment with aminophylline, and a combination of both treatments, if each treatment is carried out correctly.

It should be said at this point that a physician may apply the treatment which is the physician’s own forte after he or she has understood
the advantages and disadvantages of each treatment.

2. Other treatments

The use of antibiotics should be limited to bacterial infection and is not necessary for viral infection. Bacterial infection is differentiated from viral infection by leukocytosis, an increase in CRP, pneumonic shadow in chest x-ray, and the detection of bacteria in sputum. Generally, expectorants are not used because there is no expectorant that is more effective than corticosteroids. The use of sedatives in general is limited to use only in ICU. Large amounts of fluid should not be supplemented, which is hazardous. Supplementation of normal amounts of fluid is appropriate.

3. Laboratory examinations

Laboratory examinations are generally performed when hospitalization is needed. For such examinations, blood sampling, chest x-ray study, and expectoration test are carried out, giving particular attention to the bacterial infection of the airways, cardiopulmonary complications and blood sugar level.

Asthma Prevention

Once asthma exacerbation has developed, it is important to improve it quickly with appropriate treatment. Prevention of the development of asthma exacerbation is also important. Patient education under long-term management is essential for this purpose. Patient education includes learning about long-term management and therapies, how to recognize the early signs of asthma exacerbation using peak expiratory flow monitoring, and how to step up in pharmacologic therapy on the basis of objective indices under self-management. Detailed instruction on the use of oral corticosteroids is a critical point for successful self-management.

In addition, the factors contributing to asthma exacerbation should be pointed out and the removal or avoidance of these risk factors is advised to individual patient. It is recommended, for example, to avoid indoor pets, smoking, and drinking alcohol. It is very important to prevent acute exacerbation in this way and to avoid the development of severe exacerbation.

REFERENCES

